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Docking-based tools for discovery of protein-protein modulators and Influence of protein flexibility on Virtual Screening (V.S)

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Abstract

Protein-protein interactions (PPIs) play an essential role in the majority of cell processes, and their dysregulation, caused either by environment factors or genetic variations, are origin of many pathological conditions. Strategies to modulate PPIs with small molecules have therefore attracted increasing interest over the last years. However, the quest for

new PPI inhibitors has major difficulties, such as the usually large size of protein-protein interfaces or the absence of preformed cavities in them. These problems are especially challenging when no 3D structure is available for the protein-protein complex. By using docking simulations with pyDock, it is possible to identify protein-protein hot-spot residues, which can help to localize possible small-molecule binding sites without any

prior structural knowledge of the complex. Then, molecular dynamics (MD) can be used to describe fluctuations on the interacting surfaces, in order to search for transient cavities with Fpocket. We evaluated this approach on a small set of protein-protein complexes with known small-molecule inhibitors, in which structural data are available for the unbound molecules, as well as for the protein-protein and protein-inhibitor complexes. We found that MD simulations are essential to find small cavities that are similar to the inhibitor binding sites. The predicted hot-spot residues helped to identify the known inhibitor binding sites. We will discuss how these predicted cavities can play an interesting point for the chemical perturbation of PPIs through small-molecules.

Abstract

The drug discovery (DD) process is a slow and expensive process with high attrition rates. In the last years the computational methodologies used to study biologic systems have undergone a major improvement due to the rapid technological development. This has allowed the development and incorporation of *in silico* methodologies into the drug

discovery pipeline. One of these methodologies is the Virtual Screening (VS) where thousands of compounds are computationally studied in search of new compounds that will become commercially available drugs. Most of current methodologies treat the proteins as rigid entities but it has been shown that proteins are dynamic entities that may undergo conformational changes upon ligand binding. The focus of this talk will be how the inclusion of protein flexibility, by using the PELE simulation program, affects the VS results.

Short bio

Mireia Rosell is a PhD student at the Protein Interactions and Docking Group in the Barcelona Supercomputing Center, lead by Juan Fernandez-Recio. She did a B.Sc. In Biochemistry at Universitat Autònoma de Barcelona and afterwards she obtained an interuniversity M.Sc. in Bioinformatics for Health Sciences by Universitat Pompeu Fabra and Universitat de Barcelona. Her research is focused on the development of a new methodology for the high-throughput structural annotation of sequence variants involved in protein interactions.

Short bio

Jelisa Iglesias is a PhD student in her last year at the EAPM group in the Life Science department at the BSC.

She obtained her MsC in Bioinformatics by the UAB in 2014 and her Biotechnology degree by the UB at 2013.